Scrub Typhus and Abnormal Electrocardiography

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Abstract. This study compared the frequency of abnormal electrocardiogram (ECG) types between scrub typhus patient group and age- and gender-matched health checkup group and their associations with disease severity in scrub typhus patient. Demographic characteristics and ECG and laboratory findings of patients with scrub typhus admitted to Chosun University Hospital, and normal subjects visiting the hospital for health checkup from January 2008 to December 2012 were retrospectively studied. Electrocardiogram abnormalities at admission were observed in 72 of 165 (43.6%) scrub typhus confirmed patients. The following ECG abnormalities were observed: arrhythmic group (31 cases, 18.8%), ischemic change group (25 cases, 15.1%), prolonged QT group (32 cases, 19.4%). Compared with the age and gender-matched health checkup group, ECG abnormalities were more commonly observed in scrub typhus patient group (13.9% versus 43.6%, $P < 0.001$). In addition, when compared with the normal ECG group, scrub typhus in the abnormal ECG group showed greater disease severity and this phenomenon was particularly prominent in the prolonged QT group. Based on our study prolonged QT observed in approximately 20% of patients with scrub typhus, clinicians should pay additional attention to drugs that affect QT interval.

INTRODUCTION

Scrub typhus is an acute febrile disease characterized by systemic vasculitis that is transmitted via bites from mite larvae (chigger) infected with *Orientia tsutsugamushi*.¹ The incidence of scrub typhus is generally high in Asia, although recent outbreaks have been reported in Western countries along with the increase in international travel.^{2,3} Scrub typhus can be cured with antibiotics, if the clinical disease course is not severe, although a delayed diagnosis may lead to severe complications such as pneumonia, acute kidney injury, meningitis, encephalitis, upper gastrointestinal bleeding, and multiple organ failure, as well as the possibility of myocardial infarction or stroke, and some patients may die from such complications.⁴

Most patients with scrub typhus is known to be shown with normal electrocardiogram (ECG) findings, although some patients present with nonspecific ECG changes such as ST segment changes, T wave changes, and atrial premature beat (APB) and ventricular premature beat (VPB). On one hand, severe ECG changes such as atrial fibrillation (AFib), atrial flutter, and torsades de pointes have also been reported.⁵ However, few studies have evaluated ECG abnormalities in scrub typhus patients.

Accordingly, this study aimed to confirm the frequency of ECG abnormalities and commonly observed ECG type in the scrub typhus patients. We also tried to check the differences between the scrub typhus patients and the general population in the aspect of ECG abnormality and ascertain the relationship between ECG abnormalities and disease severity.

MATERIALS AND METHODS

Among 253 patients with scrub typhus hospitalized at Chosun University Hospital during the 5-year period from January 2008 to December 2012, 88 patients with missing

ECG records were excluded; thus, a total of 165 patients were retrospectively investigated in this study. Subjects who visited Chosun University Hospital during the same period for the purpose of health checkups served as age- and gender-matched controls at a 1:1 ratio.

The patients with scrub typhus were defined as those admitted to the hospital with characteristic eschar and typical clinical symptoms such as fever, chills, headache, and skin rash. Scrub typhus patients also exhibited > 4-fold increases in antibody titers on indirect immunofluorescent antibody tests during the recovery period or received positive diagnoses via nested polymerase chain reaction tests using material obtained from buffy coats or eschar samples.

The patients' age, gender, and underlying health factors, including cigarette smoking, hypertension (HTN), diabetes mellitus (DM), cardiovascular disease, pulmonary disease, hepatic disease, and malignancy were investigated.

The patients with a normal sinus rhythm (NSR), including sinus tachycardia during ECG at admission were classified as the normal ECG group, whereas those with ECG findings other than NSR were classified as the abnormal ECG group. The latter group was further subclassified as follows: the arrhythmia group represented with Afib, APB, VPB, and conduction delay, such as atrioventricular block, right bundle branch block, and left bundle branch block; the ischemic group represented with ST-segment changes, T wave changes, and abnormal Q waves; and the prolonged QT group.

A 12-lead ECG was obtained using a MAC 5500 machine (GE Healthcare, Little Chalfont, United Kingdom), and ECG records were classified using a modified version of the Minnesota code (Table 1).⁶

To evaluate scrub typhus severity, this study defined the patients with the following complications such as interstitial pneumonia, myocarditis, meningitis, acute respiratory distress, acute renal failure, shock, gastrointestinal bleeding, and death as serious patients.

Statistical analysis was performed using SPSS for Windows version 18.0 (SPSS, Inc., Chicago, IL). Continuous variables were described as mean values $\pm$ standard deviations, and noncontinuous variables were described as frequencies and percentages (%). Subject comparisons were performed using

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TABLE 1

Definition of abnormal electrocardiogram finding according to the modified version of the Minnesota code

Q wave	Q/R $\geq$ 1/5, Q duration $\geq$ 0.03 seconds (s)
ST segment	ST depression $\geq$ 1 mm (I, II, aVL, aVF, V1-6)
T wave	T wave $\geq$ -5 mm (I, II, V2-6), when R $\geq$ 5 mm (aVL) and QRS upright (aVF)
AV conduction	RP > 0.21 seconds (I, II, III), partial AV block, complete AV block
Ventricular conduction	QRS > 0.12 seconds
Atrial fibrillation	Atrial fibrillation present
Atrial flutter	Atrial flutter present
Premature beat	Atrial premature beat and ventricular premature beat present
Poor R progression	R wave < 2-4 mm in V3 or V4 R in V4 < R in V3, R in V3 < R in V2, R in V2 < R in V1
Long QT interval ²²	Corrected QT interval Male > 0.45 seconds, Female > 0.46 seconds

AV = atrioventricular.

one-way analysis of variance and the χ^2 test. The significance level was set at $P < 0.05$.

RESULTS

Patient characteristics. The subjects included a total of 165 patients with scrub typhus (after excluding 88 patients with missing ECG records) who were hospitalized for scrub typhus at Chosun University Hospital during the study period. The mean age was 63.3 ± 13.3 years, and the subjects included 58 men (35.2%) and 19 cigarette smokers (11.5%). The underlying diseases included 56 cases (33.9%) of HTN, 31 cases (18.8%) of DM, four cases (2.4%) of cardiovascular disease, three cases (1.8%) of pulmonary disease, 14 cases (14.9%) of hepatic disease, and eight cases (4.8%) of malignancy.

The frequency of ECG abnormality at admission in patients with scrub typhus. At admission, ECG abnormalities were observed in 72 (43.6%) of 165 patients with scrub typhus; the remaining 93 patients (56.4%) with scrub typhus showed normal ECG results, including 26 patients with sinus tachycardia. The following ECG abnormalities were observed: arrhythmia group (31 cases, 18.8%); ischemic change group (25 cases, 15.1%); and prolonged QT group (32 cases, 19.4%) (Table 2).

TABLE 2

ECG abnormality in 165 scrub typhus patients

ECG abnormalities	72 (43.6%)
Arrhythmic group	31 (18.8%)
Atrial fibrillation	15 (9.1%)
Atrial premature beat	5 (3.0%)
Ventricular premature beat	1 (0.6%)
1° AV block	6 (3.6%)
2° AV block	0 (0%)
3° AV block	1 (0.6%)
Right bundle branch block	5 (3.0%)
Left bundle branch block	1 (0.6%)
Ischemic change group	25 (15.1%)
ST depression	0 (0%)
ST elevation	1 (0.6%)
T wave inversion	21 (12.7%)
Q wave	3 (1.8%)
Poor R progression	3 (1.8%)
Prolonged QT group	32 (19.4%)

Cf > AV = atrioventricular; ECG = electrocardiogram.

Comparison of ECG abnormalities between the health checkup group and patients with scrub typhus.

A total of 165 patients with scrub typhus were compared with 165 control subjects who visited Chosun University Hospital for health checkup during the study period and were age- and gender-matched with the scrub typhus patients at a 1:1 ratio. Electrocardiogram abnormalities were more common in the patient group than in the health checkup group (43.6% versus 13.9%, $P < 0.001$), particularly in the prolonged QT group (19.4% versus 2.4%, $P < 0.001$), ischemic change group (15.2% versus 7.9%, $P = 0.039$) (Table 3). Regarding laboratory findings, compared with the health checkup group, the scrub typhus patient group showed increased white blood cell counts (WBC; $8,241 \pm 4,036/\text{L}$ versus $6,024 \pm 1,912/\text{L}$, $P < 0.001$), aspartate transaminase levels ($160 \pm 460 \text{ U/L}$ versus $26 \pm 12 \text{ U/L}$, $P < 0.001$), alanine transaminase levels ($92 \pm 108 \text{ U/L}$ versus $23 \pm 15 \text{ U/L}$, $P < 0.001$), blood urea nitrogen levels (BUN; $18.1 \pm 12.9 \text{ mg/dL}$ versus $15.08 \pm 4.0 \text{ mg/dL}$, $P = 0.004$), total bilirubin levels ($0.92 \pm 0.62 \text{ mg/dL}$ versus $0.78 \pm 0.27 \text{ mg/dL}$, $P = 0.008$), and creatinine levels ($1.14 \pm 0.64 \text{ mg/dL}$ versus $1.00 \pm 0.16 \text{ mg/dL}$, $P = 0.006$) and significantly lower platelet counts ($170 \pm 91 \times 10^6/\text{L}$ versus $261 \pm 64 \times 10^6/\text{L}$, $P < 0.001$) and hemoglobin levels ($12.6 \pm 1.7 \text{ g/dL}$ versus $13.6 \pm 1.2 \text{ g/dL}$, $P < 0.001$).

Comparison among patients with scrub typhus according to the presence of ECG abnormalities at admission.

The patients with scrub typhus in the abnormal ECG group (based on ECG findings at admission) were significantly older than those in the normal ECG group (66.2 years versus 61.1 years, $P = 0.014$) and had higher prevalence of HTN (43.1% versus 26.9%, $P = 0.03$); no significant differences in gender and underlying disease were observed between the groups.

Regarding the laboratory findings, the abnormal ECG group showed increased WBC counts, total bilirubin, BUN, and creatinine level (Table 4). Regarding the disease severity of scrub typhus patients, the abnormal ECG group showed greater disease severity compared with normal ECG group (34.7% versus 20.4%, $P = 0.04$, Table 4).

Comparison between the normal ECG group and abnormal ECG subgroups at admission in patients with scrub typhus.

In a comparison of the abnormal ECG subgroup with the normal ECG group, arrhythmia group patients were older, had a higher prevalence rate of HTN, DM and showed increased WBC, BUN, creatinine, total bilirubin, and lactate dehydrogenase; these arrhythmia group patients also showed lower levels of albumin, sodium (Na), chloride (Cl), and calcium (Ca) (Table 5).

Compared with the normal ECG group, ischemia group revealed no significant differences. However, prolonged QT group defined by corrected QT interval prolongation values > 0.45 milliseconds (ms) in men and > 0.46 ms in women, were older and showed increased WBC, BUN, creatinine level and lower levels of Ca and albumin, and more severe patients compared with normal ECG group.

DISCUSSION

Orientia tsutsugamushi is known to spread systemically through the vascular and lymphatic systems,¹ although the mechanism of infection dissemination remains unclear. In a recent murine model study, in which *O. tsutsugamushi* was injected into the right hind foot pads of mice and bacterial loads

TABLE 3

A comparison of clinical features, laboratory findings, and ECG abnormalities between the health-care checkup group and scrub typhus patients

	Health-care checkup group (n = 165)	Scrub typhus patient group (n = 165)	P value
Demographic characteristics			
Age (years)	63.33 ± 13	63.33 ± 13	1.000
Male	58 (35.2%)	58 (35.2%)	1.000
Laboratory finding			
WBC (/L)	6,024 ± 1,912	8,241 ± 4,036	< 0.001
Platelets (×10 ⁶ /L)	261 ± 64.8	170 ± 91	< 0.001
Hb (g/dL)	13.6 ± 1.2	12.6 ± 1.7	< 0.001
Aspartate transaminase (U/L)	26.3 ± 12	160 ± 460	< 0.001
Alanine transaminase (U/L)	23 ± 15.2	92 ± 108	< 0.001
Total bilirubin (mg/dL)	0.78 ± 0.27	0.92 ± 0.62	0.008
blood urea nitrogen (mg/dL)	15 ± 4.0	18 ± 12.9	0.004
Creatinine (mg/dL)	1.00 ± 0.16	1.14 ± 0.64	0.006
ECG abnormality	23 (13.9%)	72 (43.6%)	< 0.001
Arrhythmic group	21 (12.7%)	31 (18.8%)	0.131
Ischemic change group	13 (7.9%)	25 (15.2%)	0.039
Prolonged QT group	4 (2.4%)	32 (19.4%)	< 0.001

ECG = electrocardiogram; Hb = Hemoglobin; WBC = white blood cell.

were subsequently measured in each organ, after the lung, the second highest bacterial load was observed in the heart, suggesting that heart tissues may experience a greater level of *O. tsutsugamushi* bacterial invasion than other tissues.⁷

In this study, groups of scrub typhus patients were compared according to the presence or absence of ECG changes on hospital admission, which were used as indicators to assess cardiac involvement and disease severity. Abnormal ECG findings at admission were observed in 43.6% of patients

with scrub typhus, including 19.4%, 15.1%, and 12.7% of patients classified as prolonged QT group, ischemic change group and arrhythmia group, respectively. Abnormal ECG in scrub typhus patients was associated with old age and increased WBC, BUN, creatinine and total bilirubin. In addition, when compared with 1:1 age and gender-matched normal subject ECG abnormalities were much more common among scrub typhus patients (43.6% versus 13.9%). In another Thailand study, abnormal ECG was found in 39 of 79 patients

TABLE 4

A comparison of demographic and clinical characteristics, laboratory findings, and disease severity between scrub typhus patients in the normal ECG group and abnormal ECG group

	Normal ECG group (n = 93)	Abnormal ECG group (n = 72)	P value
Characteristics			
Age (years)	61.1 ± 13.2	66.2 ± 12.4	0.014
Male (%)	29 (31.2)	29 (40.3)	0.225
Underlying diseases			
Smoking (%)	10 (10.7)	9 (12.5)	0.736
Hypertension (%)	25 (26.9)	31 (43.1)	0.03
Diabetes (%)	13 (14.0)	18 (25.0)	0.072
Cardiovascular diseases (%)	2 (2.2)	2 (2.8)	0.795
Lung diseases (%)	2 (2.2)	1 (1.4)	0.716
Hepatic diseases (%)	7 (7.5)	7 (9.7)	0.795
Cancer (%)	4 (4.3)	4 (5.6)	0.710
Laboratory			
White blood cell (/L)	7,457 ± 3,430	9,253 ± 4,531	0.006
Platelets (×10 ⁶ /L)	173 ± 104	167 ± 70	0.659
Erythrocyte sedimentation rate (mm/Hour)	21.8 ± 19.3	23.8 ± 19	0.517
C-reactive protein (mg/dL)	8.3 ± 8	10.1 ± 7.3	0.153
Alkaline phosphatase (U/L)	106 ± 70	114 ± 101	0.572
Aspartate transaminase (U/L)	170 ± 553	147 ± 303	0.745
Alanine transaminase (U/L)	92 ± 108	91 ± 107	0.955
Albumin (g/dL)	3.6 ± 0.6	3.5 ± 0.6	0.216
Total bilirubin (mg/dL)	0.8 ± 0.53	1.06 ± 0.7	0.012
Blood urea nitrogen (mg/dL)	14.9 ± 9.3	22.3 ± 15.5	0.001
Creatinine (mg/dL)	1.02 ± 0.42	1.31 ± 0.82	0.007
CK-MB (ng/mL)	5.18 ± 6.5	10.3 ± 36.4	0.289
Troponin-T (ng/mL)	0.014 ± 0.13	0.016 ± 0.13	0.447
N-terminal probrain natriuretic peptide (pg/mL)	150 ± 46	3,397 ± 3,793	0.115
Na (mEq/L)	137 ± 4.7	136 ± 4.3	0.073
K (mEq/L)	3.9 ± 0.47	3.9 ± 0.53	0.802
Cl (mEq/L)	104 ± 4.8	103 ± 5.7	0.139
Lactate dehydrogenase (U/L)	610 ± 316	685 ± 488	0.255
Ca (mg/dL)	8.18 ± 0.53	8.00 ± 0.63	0.141
Mg (mg/dL)	2.09 ± 0.38	2.07 ± 0.38	0.850
Phosphate (mg/dL)	3.07 ± 1.06	3.24 ± 1.16	0.490
Severe scrub typhus (%)	19 (20.4)	25 (34.7)	0.04

ECG = electrocardiogram.

TABLE 5

A comparison of demographic and clinical characteristics, laboratory findings and disease severity between scrub typhus patients in the normal ECG group and abnormal ECG subgroup

	Normal ECG group		Abnormal ECG Subgroup		
	(n = 93)	Prolonged QT (n = 32)	P value	Arrhythmia (n = 31)	P value
Characteristics					
Age (years)	61.1 ± 13.2	67.6 ± 11.9	0.016	67.5 ± 12.3	0.019
Male (%)	29 (31.2)	15 (46.9)	0.109	17 (54.8)	0.018
Underlying diseases					
Smoking (%)	10 (10.7)	3 (9.4)	0.859	4 (12.9)	0.956
Hypertension (%)	25 (26.9)	12 (37.5)	0.256	16 (51.6)	0.011
Diabetes (%)	13 (14.0)	8 (25.0)	0.150	10 (32.3)	0.023
Cardiovascular diseases (%)	2 (2.2)	2 (6.3)	0.256	1 (3.2)	0.736
Lung diseases (%)	2 (2.2)	1 (3.1)	0.756	0 (0.0)	0.410
Hepatic diseases (%)	7 (7.5)	4 (12.5)	0.475	3 (9.7)	0.912
Cancer (%)	4 (4.3)	1 (3.1)	0.770	2 (6.5)	0.629
Laboratory					
White blood cell (/L)	7,457 ± 3,430	10,388 ± 4,874	0.001	9,930 ± 5,336	0.02
Platelets (×10 ⁶ /L)	173 ± 104	184 ± 67	0.583	159 ± 74	0.496
Erythrocyte sedimentation rate (mm/Hour)	21.8 ± 19.3	25.2 ± 20.4	0.403	25.6 ± 20.4	0.368
C-reactive protein (mg/dL)	8.3 ± 8	10.9 ± 7.6	0.113	11.5 ± 6.4	0.053
Alkaline phosphatase (U/L)	106 ± 70	119 ± 112	0.477	105 ± 96.7	0.936
Aspartate transaminase (U/L)	170 ± 553	180 ± 440	0.930	139 ± 146	0.756
Alanine transaminase (U/L)	92 ± 108	89 ± 127	0.894	97 ± 101	0.830
Albumin (g/dL)	3.6 ± 0.6	3.4 ± 0.6	0.044	3.4 ± 0.6	0.055
T-bilirubin (mg/dL)	0.8 ± 0.53	1.02 ± 0.57	0.057	1.06 ± 0.57	0.026
Blood urea nitrogen (mg/dL)	14.9 ± 9.3	24.7 ± 17.5	0.004	22.5 ± 14.6	0.009
Creatinine (mg/dL)	1.02 ± 0.42	1.41 ± 1.06	0.048	1.24 ± 0.49	0.014
CK-MB (ng/mL)	5.18 ± 6.5	14.4 ± 51	0.348	7.39 ± 14.5	0.307
Troponin-T (ng/mL)	0.014 ± 0.13	0.016 ± 0.014	0.466	0.016 ± 0.015	0.414
N-terminal probrain natriuretic peptide (pg/mL)	150 ± 46	4,106 ± 4,733	0.05	4,980 ± 5,189	0.109
Na (mEq/L)	137 ± 4.7	136 ± 3.9	0.130	134 ± 4.3	0.001
K (mEq/L)	3.9 ± 0.47	3.95 ± 0.53	0.877	4.0 ± 0.59	0.548
Cl (mEq/L)	104 ± 4.8	103 ± 5.5	0.247	102 ± 5.6	0.013
Lactate dehydrogenase (U/L)	610 ± 316	726 ± 594	0.181	752 ± 417	0.063
Ca (mg/dL)	8.18 ± 0.53	7.86 ± 0.55	0.038	7.87 ± 0.45	0.022
Mg (mg/dL)	2.09 ± 0.38	2.12 ± 0.38	0.739	2.07 ± 0.35	0.897
Phosphate (mg/dL)	3.07 ± 1.06	3.39 ± 1.38	0.329	3.11 ± 1.16	0.886
Severe scrub typhus (%)	19 (20.4)	13 (40.6)	0.024	8 (25.8)	0.530

ECG = electrocardiogram.

(49.4%), including sinus tachycardia (17 patients, 21.5%), new onset Afib (nine patients, 11.3%).⁸

In a Papua New Guinea study conducted in 1945, no significant ECG changes were observed in patients with scrub typhus⁹; a study conducted in Thailand in 2002 revealed that mild ECG changes (e.g., ST-T change, U wave, VPB) were observed in only 24% of patients.¹⁰ However, in this study, ECG abnormalities were observed in 72 (43.6%) of 165 scrub typhus patients and this result is higher than previous report by Kim et al.,¹¹ where ECG abnormalities were observed in about one-third of scrub typhus patients. Therefore, ECG abnormalities were observed in a considerable number of scrub typhus patients in this study compared with previous studies. Whether this difference in frequency is due to differences in virulence related to the *O. tsutsugamushi* genotype or serotype or to differences in racial sensitivity is unclear. The subjects of the study conducted in Papua New Guinea [9] were mostly military personnel and thus likely comprised relatively young men, although their ages were not indicated. Moreover, as the mean age of patients with scrub typhus in the study from Thailand was 39 years [10], influences related to age or underlying disease would likely explain the observed differences in the frequency of ECG abnormalities.¹²

Atrial fibrillation was the most commonly observed type of arrhythmia observed in patients with scrub typhus. In Korea,

the reported prevalence rates of Afib were 0.7% in people aged ≥ 40 years, 2.1% in people aged ≥ 65 years, and 4.0% in people aged ≥ 80 years.¹³ In this study, the health checkup group had a mean age of 63 years and showed an 1.8% Afib prevalence, whereas the scrub typhus patients group showed a higher Afib prevalence of 9.1% ($P = 0.004$) despite a lack of difference in age.

The mechanism by which ECG changes occur in patients with scrub typhus has not yet been clearly determined. However, various cardiac complications, such as myocarditis,¹⁴ myocardial infarction,¹⁵ and pericarditis¹⁶ have been reported in patients with scrub typhus. *Orientia tsutsugamushi* may proliferate and induce apoptosis in the microvascular endothelium, leading to vasculitis and perivasculitis in multiple organs systemically. Particularly, the most remarkable change occurs in the interventricular septum of the heart, and both focal and general myocarditis have been reported. However, because involvement of the coronary artery and heart valve is very rare and no severe cardiac myofibril damage has been observed, chronic heart damage is known to rarely occur, similar to other rickettsial diseases.¹⁷

It is possible that ECG abnormalities in patients with scrub typhus may be caused by an electrolyte imbalance or fever, in addition to cardiac abnormalities. Woodward et al.¹⁸ reported that low-voltage QRS abnormalities and Afib on ECG might be suggestive of myocardial damage. However, a prospective

study conducted in Taiwan found no differences in QRS wave abnormalities between patients with scrub typhus and normal subjects; this study also showed that 17 and 14 of 27 patients with scrub typhus had low serum potassium concentrations during the febrile and recovery periods, respectively, suggesting a possible relationship between hypokalemia and ECG abnormalities.¹⁰ Furthermore, a study by Kim et al. found high BUN in patients with arrhythmia at admission and high BUN and creatinine levels in patients with abnormalities during follow-up ECG, suggesting that an electrolyte imbalance or increased creatinine level is likely to be associated with ECG changes.¹¹ In the present study, BUN and creatinine levels were significantly higher in patients with abnormal ECG findings, whereas serum sodium (134.3 mEq/L versus 137.3 mEq/L, $P = 0.008$) and calcium levels (7.84 mg/dL versus 8.18 mg/dL, $P = 0.023$) were low in patients with scrub typhus in the arrhythmia group. In particular, the most common ECG abnormality, QT prolongation, is known to be induced by various drugs or electrolyte abnormalities (e.g., hypokalemia, hypomagnesemia, and hypocalcemia) and can cause severe ventricular arrhythmias, such as torsade de pointes.^{5,19,20} Surprisingly, the finding of this study suggesting that QT prolongation was most prevalent is very important clinically. Torsade de pointes, a life-threatening arrhythmia, was reported to have occurred in patients with scrub typhus receiving azithromycin.²¹ If patients with QT prolongation are given macrolide or quinolone antibiotics, which can cause QT prolongation, ventricular arrhythmia may occur; therefore, caution is required when using these aforementioned drugs. In addition to drugs, QT prolongation may be induced by an electrolyte imbalance. Among scrub typhus patients, the prolonged QT group showed lower total calcium (7.86 mg/dL versus 8.18 mg/dL, $P = 0.038$) and ionized calcium levels than the normal ECG group (4.09 mg/dL versus 4.27 mg/dL, $P = 0.018$). Therefore, we believe that systematic studies of the causes of hypocalcemia in patients with scrub typhus, as well as the relationship with ECG abnormalities such as QT prolongation, are needed in the future.

Although the symptoms used to assess severity in patients treated for scrub typhus include hypotension, thrombocytopenia, leukocytosis, acute kidney injury, hypoalbuminemia, and hepatic injury, the initial ECG findings are often overlooked. A study by Kim et al.¹¹ suggested that initial ECG finding abnormalities might be related to uremia or admission into the intensive care unit and, accordingly, that ECG findings at the time of patient admission should be carefully checked, as continued follow-up is required if an ECG abnormality is found. In the present study, ECG abnormalities at admission were implicated in disease severity, especially in prolonged QT group, although there was no significant difference in arrhythmic group. So an ECG abnormality is considered a possible manifestation of severe disease.

The present study had certain limitations, including its retrospective study design and single-institution setting. The second, many patients were transferred from other hospitals for failure to respond to treatment or comorbidities, and it may therefore be difficult to generalize the subjects of this study to the entire patient population. The third, for most cases, pre-admission ECG findings were unknown, and in many cases, it was difficult to accurately determine whether the abnormal ECG findings at admission were actually associated with

scrub typhus. The fourth, the use of QTc prolongation agents in all patients included in this study was not fully investigated because it is retrospective study. However, almost all possible scrub typhus patients included in this study were initially checked whether the antibiotics such as macrolide, quinolone were not administered before admitted to Chosun University Hospital or not.

Nevertheless, this was the first study to compare the frequencies of different types of ECG abnormalities between patients with scrub typhus and controls on a large scale. This study demonstrated that ECG abnormalities were more commonly observed in patients with scrub typhus than in the control health checkup group. In addition, patients with scrub typhus who presented with prolonged QT interval at admission showed greater disease severity than normal ECG group. Thus, clinicians must pay more attention when administering antibiotics that may prolong QT interval.

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